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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,652	SRIVASTAVA ET AL.	
	Examin r	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-19,21 and 32-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-19,21 and 32-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, remarks, exhibits and IDS, filed 9/22/03, are acknowledged.

2. Claims 1-2, 6-19, 21, 32, and newly added Claims 33-52 are under examination.

3. In view of Applicant's amendment and remarks, all previous rejections have been withdrawn. Regarding the previous rejection under 35 U.S.C. 112, second paragraph, based on the interview of 9/17/03 and the instant remarks, it is the Examiner's understanding that Claims 16-18 and newly added Claims 46-48 are intended to mean that the amount of total HSP:peptide complex administered to any mammal at any one time would be between 5 μg and 5,000 μg (Claims 16 and 46), more than 100 μg (Claims 17 and 47), and more than 200 μg (Claims 18 and 48). Regarding the previous rejection under 35 U.S.C. 103(a), Applicant has repeatedly argued that in the context of immunosuppression (which would be used to treat or prevent) graft rejection, heat shock proteins (HSPs) cannot be considered to be interchangeable and that data obtained using one HSP (for example HSP60) cannot be considered to be an indicator of how any other HSP would act in the instant context.

4. The following are new grounds for rejection.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically, the claim is in improper multiple dependent form.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2, 6-19, 21, 32, and newly added Claims 33-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for inhibiting the rejection of BALB/cJ skin when transplanted onto a C57BL/6 mouse, said method comprising administering to a C57BL/6 mouse gp96 purified from a BALB/cJ source, said administration comprising subcutaneous injection of 100 μg 10 days prior to transplantation, repeated 3 days prior to transplantation,

does not reasonably provide enablement for:

a method for treating or preventing rejection of a grafted cell, tissue, or organ in a mammal comprising administering to a mammal a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cell, tissue, or organ.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding a method of treating or preventing graft rejection by administering HSPs, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the medical arts are such that

little is known regarding treating or preventing graft rejection by administering HSPs. Indeed, the Inventor himself has repeatedly taught that in numerous contexts, both *in vitro* and *in vivo*, *all* heat shock proteins are immunostimulatory (see for example, U.S. Patents No. 5,985,270, 5,750,119, and 5,961,979). Accordingly, claims based on the highly unexpected assertion that HSPs are sometimes immunosuppressive when administered *in vivo*, require enablement commensurate with the scope of the claims.

Regarding the scope of the claims, it is noted that said claims encompass the claimed method employing *all* HSPs (except hsp60 and cpn10) which Applicant has repeatedly argued (and demonstrated with sequence alignments) are *not* related and are *not* interchangeable. Clearly then, given the highly unexpected nature of the instant invention, said invention cannot be considered to be enabled for any HSP not demonstrated (in the specification or art) to be immunosuppressive in the instant context (graft rejection). It is noted that the specification discloses only the use of BALB/cJ mouse and unknown rat gp96, and only in the context of transplant into a C57BL/6 mouse. The results of Experiment 2 demonstrate that rat gp96 treatment worked little (if any) better than control (no) treatment in the instant method. Accordingly, not even all gp96's (even those likely to be closely related) can be considered to be enabled. The most likely conclusion to be drawn from the limited data is that the gp96 must derive from the same genetic source as the graft. Also note that in no case was graft rejection ever "prevented" as claimed.

A review of the specification discloses that the maximum disclosed dosage range is "about 5 μg to about 5000 μg" of complex (page 31). There is no disclosure in the specification of any dosage greater than "about 5000 μg" in any context. The specification also discloses that a 20-25 g mouse is administered 100-200 μg of complex; the specification also demonstrates that lesser dosages are ineffective (see Experiments 1 and 2). As a human is roughly 3000 times the size of a mouse, the appropriate dosage for a human would likely be 300,000-600,000 μg of complex - at least 60 times higher than the highest dosage disclosed by the specification. As a horse or cow is roughly 10 times the size of a human, the maximum disclosed dosage would likely fall 600 times short of what would be required to be effective in said mammals.

It is the Examiner's position then that given the broad scope of the claims and the limited working examples, the

specification cannot be considered enabling for the invention as claimed.

Applicant has submitted WO 02/072133 as enablement for "HSP70 family members" in the method of the instant claims. Upon review said document cannot be considered enabling for the use of HSP70 family members in the method of the instant claims. The document discloses the use of BiP (a HSP70) only in a highly artificial arthritis model. Presumably, Applicant's argument is that artificial arthritis and graft rejection are both TH1-mediated, thus a treatment for the artificial arthritis model would be effective as a treatment for graft rejection. The document indicates that BiP has an immunosuppressive effect because it stimulates IL-10 release (page 8) which induces an anti-inflammatory shift towards TH2 (page 23). This capability of inducing IL-10 release and the subsequent shift towards TH2 is presumably how BiP might function in inhibiting graft rejection. There exists however, a significant body of work indicating that IL-10 is not necessarily immunoprotective, a shift towards TH2 is not necessarily desirable, and a HSP70 might actually be a facilitator in numerous models of TH1-mediated pathology. See for example, Pakala et al. wherein it is taught that in a disease model thought to be TH1-mediated, induction of IL-10 and a TH2 response, rather than being protective or benign, was highly pathogenic. The work calls into question the entire concept of a shift towards TH2 as a treatment of TH1 pathologies. See also McFarland, wherein as early as 1996 it was taught the "Mechanisms of autoimmunity [and presumably graft rejection] are more complicated than a simple TH1-Th2 dichotomy". The reference further teaches additional instances wherein the TH2 response worsens diseases thought to be TH1 mediated. As regards an HSP70 family member specifically, Mycko et al. teaches the enhancement of another TH1 mediated disease by over-expression of HSP70 and increased Class II presentation of an autoantigen. The combined references indicate that at best, the use of a HSP70 in a method of inhibiting a TH1-mediated response [including graft rejection] must be considered to be highly unpredictable.

In the specific context of allograft reaction, Pockley teaches that "the balance between protective and damaging effects [of HSPs] and the precise influence of these responses on graft outcome is unclear". In some instances HSPs appear to promote the development of acute and chronic graft rejection whereas in other instances heat shock proteins appear to be cytoprotective. The reference concludes that "The role of heat shock proteins in allograft immunity is unclear and more insight into the processes

by which heat shock proteins encounter and are recognized by the recipient immune system after transplantation is required." Clearly then, the reference serves to define the invention of the instant claims as being unpredictable.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 34-39 and 42-51 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically the limitation of Claim 34, a method "wherein the heat shock protein is a member of the hsp70 family of heat shock proteins" is not supported by the specification or claims as filed.

Applicant states that support for the new limitation can be found at pages 7-11 of the specification. However, a review of the specification reveals support for "hsp70" but not for "a member of the hsp70 family" in the method of the claims.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

Please Note: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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2/22/04
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